

**PALM INTRANET**Day : Monday
Date: 3/1/2004
Time: 19:49:15

Inventor Information for 10/057620

Inventor Name	City	State/Country
SCARIA, ABRAHAM	FRAMINGHAM	MASSACHUSETTS
WADSWORTH, SAMUEL C.	SHREWSBURY	MASSACHUSETTS

Appln Info	Contents	Petition Info	Atty/Agent Info	Continuity Data	Foreign Data	I
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Search Another: Application# Search or Patent# SearchPCT / / Search or PG PUBS # SearchAttorney Docket # SearchBar Code # Search

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(FILE 'HOME' ENTERED AT 19:35:54 ON 01 MAR 2004)

FILE 'MEDLINE, CANCERLIT, BIOTECHDS, EMBASE, CAPLUS, BIOSIS' ENTERED AT
19:36:24 ON 01 MAR 2004

L1	105 S FACTOR VII AND GENE THERAPY
L2	6313 S FACTOR VIIA
L3	33 S L1 AND L2
L4	31 DUP REM L3 (2 DUPLICATES REMOVED)
L5	470600 S CLEAVAGE OR CLEAVED
L6	3 S L5 AND L1
L7	2 DUP REM L6 (1 DUPLICATE REMOVED)
L8	4260 S FURIN
L9	2 S L8 AND L1
L10	2 DUP REM L9 (0 DUPLICATES REMOVED)

=>

Nguyen, Dave

From: Auto TrainR
Sent: Wednesday, February 25, 2004 9:47 AM
To: Nguyen, Dave
Cc: Reynolds, Deborah
Subject: Class Registration Confirmation for Dave Nguyen

Dear Dave Nguyen,

This is to confirm that you have registered for the following class:

Course Title: End of the Year Review of CAFC Decisions (1.5hr)
Date: Thu Mar 04, 2004
Time: 02:30 PM
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Registered As: SPE Assigned

Have a nice day!

The Patent Automation Training Team
Tel: (703) 306-5791 & (703) 306-5792
E-mail: AutoTrainR@uspto.gov

4 ANSWER 30 OF 31 MEDLINE on STN

AN 2001222853 MEDLINE

DN PubMed ID: 11127866

TI Blocking the initiation of coagulation by RNA aptamers to **factor VIIa**.

AU Rusconi C P; Yeh A; Lysterly H K; Lawson J H; Sullenger B A

CS Department of Surgery, Duke University Medical Center, Durham, NC 27710, USA.

SO Thrombosis and haemostasis, (2000 Nov) 84 (5) 841-8.
Journal code: 7608063. ISSN: 0340-6245.

CY Germany: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200104

ED Entered STN: 20010502
Last Updated on STN: 20010502
Entered Medline: 20010426

AB The tissue factor/**factor VIIa** complex is thought to be the primary initiator of most physiologic blood coagulation events. Because of its proximal role in this process, we sought to generate new inhibitors of tissue factor/**factor VIIa** activity by targeting **factor VIIa**. We employed a combinatorial RNA library and in vitro selection methods to isolate a high affinity, nuclease-resistant RNA ligand that binds specifically to coagulation **factor VII/VIIa**. This RNA inhibits the tissue factor-dependent activation of factor X by **factor VIIa**. Kinetic analyses of the mechanism of action of this RNA suggest that it antagonizes **factor VIIa** activity by preventing formation of a functional **factor VII**/tissue factor complex. Furthermore, this RNA significantly prolongs the prothrombin time of human plasma in a dose dependent manner, and has an in vitro half-life of approximately 15 h in human plasma. Thus, this RNA ligand represents a novel class of anticoagulant agents directed against **factor VIIa**.

L4 ANSWER 28 OF 31 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
 AN 2002:220527 BIOSIS
 DN PREV200200220527
 TI Long-term expression of activated FVII in vivo following AAV-mediated
 liver gene transfer: Implications for treatment with continuous infusion
 of recombinant activated FVII.
 AU Margaritis, Paris [Reprint author]; Arruda, Valder R. [Reprint author];
 High, Katherine A. [Reprint author]
 CS Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, USA
 SO Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 696a. print.
 Meeting Info.: 43rd Annual Meeting of the American Society of Hematology,
 Part 1. Orlando, Florida, USA. December 07-11, 2001. American Society of
 Hematology.
 CODEN: BLOOAW. ISSN: 0006-4971.
 DT Conference; (Meeting)
 Conference; Abstract; (Meeting Abstract)
 Conference; (Meeting Poster)
 LA English
 ED Entered STN: 3 Apr 2002
 Last Updated on STN: 3 Apr 2002
 AB A current treatment for acute bleeding episodes in hemophilia A and B
 patients who have developed inhibitory antibodies to the infused factor
 (factor VIII and factor IX, respectively), is administration of high doses
 of recombinant activated human **factor VII** (rFVIIa).
 While repeated bolus injections of rFVIIa have been used, experience with
 continuous infusion of rFVIIa is limited and raises safety concerns
 regarding occlusive vascular complications resulting from activation of
 the coagulation system. Here, we investigated the effect of long-term
 continuous expression of FVIIa in mice at various circulating levels, as
 part of a **gene therapy** strategy for treatment of
 hemophilic animals with inhibitors. We engineered a FVII variant that is
 intracellularly-processed and secreted as activated FVII (FVIIa), by
 inserting a protein recognition sequence for an intracellular protease at
 position Arg 152-Ile 153. This FVII variant is predominantly secreted in
 vitro in a double chain, activated FVII form and has similar in vitro
 activity and in vivo half-life as recombinant FVIIa, following injection
 in normal C57BL/6 mice. In order to demonstrate the efficacy of our gene
 transfer approach, we initially used rFVIIa into hemophilia A and B mice
 with and without inhibitors, injected at the clinically effective dose of
 90 micrograms/kg. We observed a shortening of the prothrombin time (an
 assay sensitive to FVIIa levels) as early as 15 min, which returned to
 baseline after 6 hours, indicating that our approach can be used in a
 hemophilic mouse model. To further study the long-term effect of
 continuous FVIIa expression, we constructed a recombinant AAV-2 viral
 vector carrying this FVIIa transgene under the control of a liver-specific
 promoter and injected vector into the portal circulation in hemostatically
 normal immunodeficient mice (n=7) at doses ranging from 1.5X10¹¹ vector
 genomes (v.g.)/mouse to 2.4X10¹² v.g./mouse. Mouse plasma was collected
 and assayed for antigen levels by an ELISA specific for human FVII/FVIIa.
 Following gene transfer, we observed stable, long-term expression of FVIIa
 with antigen levels ranging from 150 ng/ml to 950 ng/ml, as assayed over a
 period as long as 24 weeks post-injection. Throughout the course of these
 experiments, we did not observe any adverse effects at any doses tested.
 To further investigate any changes in the activity of the coagulation
 system in these animals, we assayed plasma samples collected at time
 points up to 24 weeks for the presence of elevated levels of
 thrombin-antithrombin III (TAT) complexes. By using an ELISA for TAT that
 is known to cross-react with murine proteins, we observed TAT levels
 ranging from 0.8 ng/ml to 20.1 ng/ml, while TAT levels in normal animals
 were approximately 22 ng/ml. This indicates that the long-term expression
 of the FVIIa transgene did not result in detectable changes in the mouse
 coagulation system. Overall, we show that long-term expression of FVIIa
 can be achieved by AAV gene transfer without thrombotic complications.

More extensive testing will be required to demonstrate the efficacy of such therapeutic strategy in hemophilic animals with inhibitors. These data support the potential of such an approach for hemophilic patients with inhibitors.

L4 ANSWER 27 OF 31 CAPLUS COPYRIGHT 2004 ACS on STN
 AN 2001:713370 CAPLUS
 DN 135:277991
 TI Modified blood clotting factors for treatment of bleeding or clotting disorder
 IN High, Katherine A.; Margaritis, Paris; Camire, Rodney M.
 PA Children's Hospital of Philadelphia, USA
 SO PCT Int. Appl., 55 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001070763	A1	20010927	WO 2001-US9355	20010322
	W:				
	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW:				
	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRAI US 2000-191331P P 20000322

AB The invention provides compns. including modified blood clotting factors, i.e., **Factor VII**, Factor IX, and Factor X, that have a non-native proteolytic cleavage site engineered into them allowing intracellular cleavage and secretion of an active form. The compns. are useful in the methods for treating a bleeding or clotting disorder. For example, gene transfer of modified blood coagulation **factor VIIa** using the AAV-hAAT-ApoE-FVIIa expression vector offers a treatment for hemophilia patients and does not appear to induce production of inhibitory antibodies against FVIIa.

L4 ANSWER 24 OF 31 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN 2003-00809 BIOTECHDS
TI Promoting blood coagulation for treating individuals with blood
coagulation defects, e.g. hemophilia A and B, comprises administering a
DNA vector encoding a modified **Factor VII** leading to
the generation of **Factor VIIa** in vivo;
adeno virus, adeno-associated virus, retro virus or lenti virus
vector-mediated gene transfer and expression in host cell for use in
blood disease therapy and **gene therapy**

AU SCARIA A; WADSWORTH S C
PA GENZYME CORP
PI WO 2002055110 18 Jul 2002
AI WO 2001-US51391 25 Oct 2001
PRAI US 2001-307492 24 Jul 2001; US 2000-243046 25 Oct 2000
DT Patent
LA English
OS WPI: 2002-583644 [62]
AB DERWENT ABSTRACT:

NOVELTY - Promoting blood coagulation in an individual with a blood
coagulation defect, comprising administering to the individual a DNA
vector encoding a modified **Factor VII**, which leads to
generation of **Factor VIIa** in vivo, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the
following: (1) treating an individual having a blood coagulation defect
by administering a composition comprising a first DNA vector which
encodes amino acids 1-152 of human **Factor VII**, and a
second DNA vector comprising amino acids 153-406 human **Factor**
VII and a leader sequence; (2) treating hemophilia in an
individual who has developed an inhibitor of Factor VIII or Factor IX by:
(a) administering a DNA vector encoding modified **Factor**
VII, which leads to generation of **Factor VIIa**
in vivo; or (b) administering a composition comprising a first DNA vector
which encodes amino acids 1-152 of human **Factor VII**,
and a second DNA vector comprising amino acids 153-406 of human
Factor VII and a leader sequence; (3) a DNA expression
vector comprising nucleic acid encoding a modified **Factor**
VII, which leads to generation of **Factor VIIa**
in vivo; (4) a nucleic acid construct comprising two DNA expression
cassettes which together encode **Factor VII**, where the
first expression construct encodes amino acids 1-152 of human
Factor VII and the second expression encodes amino
acids 153-406 of human **Factor VII** and a leader
sequence; and (5) a nucleic acid construct comprising a polycistronic
expression cassette, where the expression cassette comprises nucleic
acids encoding the light and heavy chain of **Factor VII**
, where the nucleic acids are separated by an internal ribosome entry
site.

WIDER DISCLOSURE - Disclosed are host cells comprising a DNA vector
with a nucleic acid which encodes a modified **Factor VII**
, which leads to generation of **Factor VIIa** in vivo.

BIOTECHNOLOGY - Preferred Method: The modified **Factor**
VII in the method of promoting blood coagulation further
comprises an amino acid sequence which codes for a signal for precursor
cleavage by a cleavage enzyme selected from furin and SK1, at the
activation cleavage site of the modified **Factor VII**.
When the cleavage enzyme is furin, the amino acid sequence of the signal
in the modified **Factor VII** is selected from
Arg149-X150-Lys151-Arg152 of human FVII and Arg149-X150-Arg151-Arg152 of
human FVII, preferably Arg149-Gln150-Lys151-Arg152 of human FVII. The
leader sequence in the method of treating an individual having a blood
coagulation defect, is derived from a protein selected from a cytokine,
growth factor, colony stimulating factor and a clotting factor. The DNA
vector, administered as naked DNA or in association with an amphiphilic

compound, is a viral vector selected from an adenovirus vector, a partially-deleted adenovirus vector, a fully-deleted adenovirus vector, an adeno-associated virus vector, a pseudoadenovirus vectors, a retrovirus vector and a lentivirus vector. The blood coagulation defect is selected from hemophilia A, hemophilia B and **factor VII** deficiency, preferably hemophilia A and B, and the individual having the disease exhibits the presence of inhibitors of FVIII and/or FIX. The DNA vector in the method of treating hemophilia in an individual who has developed an inhibitor of Factor VIII or IX comprises a nucleotide sequence which codes for a signal for precursor cleavage by furin at the activation cleavage site of the modified **Factor VII**. The DNA vector is administered as naked DNA or in association with an amphiphilic compound.

ACTIVITY - Hemostatic. Test details are described but no results given.

MECHANISM OF ACTION - **Gene therapy;**
Factor-VII-Stimulator.

USE - The methods and compositions of the present invention are useful for treating an individual having a blood coagulation defect, e.g. **Factor VII** deficiency, hemophilia A and B (claimed).

ADMINISTRATION - The dose range of plasmid DNA is 1 microg-1 g, preferably 100 microg-100 mg. The dosage may also be tailored in order to achieve a FVII plasma concentration level of 5-1000 ng/ml. Routes of administration of the modified FVII include intravenous, parenteral, intramuscular, subcutaneous, oral, nasal, inhalational, by implants and/or rectal.

ADVANTAGE - Prior methods of treating bleeding disorders has led to the development of inhibitors to **Factor VII**, which can lead to the ineffectiveness of protein replacement or gene replacement therapies. Other methods using recombinant activated **Factor VII** have been shown to bypass or correct the coagulation defects in hemophiliacs with inhibitors. However, recombinant FVIIa is expensive to manufacture and has a very short half life. The present method using activated FVII delivered via DNA vectors is useful specifically to patients who have developed inhibitors especially to FVII. (44 pages)

L4 ANSWER 25 OF 31 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN 2002-09973 BIOTECHDS
TI New albumin fusion proteins with extended shelf life, useful for treating leukemia, warts, hepatitis, multiple sclerosis and AIDS, comprises therapeutic protein fused to albumin;
recombinant protein gene production via plasmid expression in host cell, polymerase chain reaction, gel electrophoresis useful in disease **gene therapy**

L7 ANSWER 2 OF 2 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
AN 2002-02325 BIOTECHDS
TI Mutant blood clotting factors useful for treating a bleeding or clotting disorder in a subject, comprising a modified proteolytic **cleavage** site not normally present in the factor;
useful for transgenic animal production and **gene therapy**
AU High K A; Margaritis P; Camire R M
PA Child.Hosp.Philadelphia
LO Philadelphia, PA, USA.
PI WO 2001070763 27 Sep 2001
AI WO 2001-US9355 22 Mar 2001
PRAI US 2000-191331 22 Mar 2000
DT Patent
LA English
OS WPI: 2001-611468 [70]
AB A composition (M) comprising a recombinant polynucleotide (I) that encodes a modified blood clotting factor (MBCF), where the modification comprises a proteolytic **cleavage** site not normally present in the factor, and where the factor is **cleaved** at the **cleavage** site when expressed in an animal cell, is claimed. Also claimed are: a polypeptide (II) encoded by (I); and a kit (II) comprising (M) or (II). Also claimed are: cells encoding (I); and vector incorporating (I). (I) is useful for treating a bleeding or clotting disorder of a subject preferably mammal especially human, having or at risk of having such a disorder, amenable to treatment with **Factor -VII**, Factor-VIII or Factor-IX and is caused by insufficient activity of expression of a vitamin-K dependent procoagulant, or by insufficient platelet aggregation. The disorder comprises hemophilia comprising hemophilia A or B, or **Factor-VII** deficiency, Glanzmann's thrombasthenia or Bernard-Soulier's thrombasthenia. (I) is also useful for decreasing clotting time and for reducing the frequency or severity of bleeding in a subject (claimed).
(55pp)

Freeform Search

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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ

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<u>L13</u>	l11 and l7	566	<u>L13</u>
<u>L12</u>	L11 same l8	0	<u>L12</u>
<u>L11</u>	factor VII	2160	<u>L11</u>
<u>L10</u>	L9 and l8	1	<u>L10</u>
<u>L9</u>	cleaved or cleavage	121175	<u>L9</u>
<u>L8</u>	l7 with l6	105	<u>L8</u>
<u>L7</u>	gene therapy	39697	<u>L7</u>
<u>L6</u>	factor VIIa	2292	<u>L6</u>
<u>L5</u>	L4 with l2	32	<u>L5</u>
<u>L4</u>	replication defective or replication incompetent	6146	<u>L4</u>
<u>L3</u>	replication defective replication incompetent	10	<u>L3</u>
<u>L2</u>	immunomodulatory or cytokine	43625	<u>L2</u>
<u>L1</u>	6287557	6	<u>L1</u>

END OF SEARCH HISTORY

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L8: Entry 105 of 105

File: DWPI

Nov 7, 2002

DERWENT-ACC-NO: 2003-428756

DERWENT-WEEK: 200340

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Full - [FULL]
Title - [TIT]
Creation - [CIT]
TITLE: Method of inhibiting immune response of host to a gene therapy vector and encoded transgene product, thus allowing persistent expression of transgene, comprises co-administering gene therapy vector with rapamycin

Basic Abstract Text (5):

Front - [FRO]
Review - [REV]
Classification - [CLAS]
Date - [DATE]
Reference - [REF]
Sequences - [SEQ]
USE - The method is useful for inhibiting immune response of host to a gene therapy vector (such as an adenoviral vector containing a deletion of adenoviral gene sequences) and encoded gene product such as glucocerebrosidase, alpha-glucosidase A, beta glucosidase, sphingomyelinase, iduronate sulfatase, alpha-glucosidase, alpha -iduronidase, Factor VIIA, Factor VIII, or Factor IX. The method thus allows for persistent expression of a transgene encoding any one of above mentioned gene products (claimed). The method has application in treatment protocols of genetic disease patients that mount immune response to protein replacement therapies.

Basic Abstract Text (7):

Attachments - [ATT]
Claims - [CLM]
KWIC - [KWIC]
Draw Desc - [DRAW]
Image - [IMG]
Preferably, the method is useful for inhibiting immune response in a patient administered with a gene therapy vector, gene therapy vector for treating lipid storage disorders such as lipid storage disorders (LSDs), e.g. Gaucher's disease, Fabry's disease, Niemann-Pick B disease, Morquio's disease, Morquio's disease, Maroteaux-Lamy disease, Pompe's disease, Hurler's-Scheie's disease in its various clinical manifestations, as well as hemophiliac factors: factor VIIA, factor VIII and factor IX.

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L15: Entry 4 of 15

File: PGPB

Dec 11, 2003

PGPUB-DOCUMENT-NUMBER: 20030229036

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030229036 A1

TITLE: Methods for treating blood coagulation disorders

PUBLICATION-DATE: December 11, 2003

US-CL-CURRENT: 514/44APPL-NO: 10/ 057620 [PALM]

DATE FILED: October 25, 2001

RELATED-US-APPL-DATA:

Application is a non-provisional-of-provisional application 60/243046, filed October 25, 2000,

Application is a non-provisional-of-provisional application 60/307492, filed July 24, 2001,

[0001] This application claims the benefit of priority under 35 U.S.C. .sctn.119(e) to U.S. Provisional Application Serial No. 60/243,046 filed Oct. 25, 2000 and No. 60/307,492 filed Jul. 24, 2001 respectively. The contents of these applications are hereby incorporated by reference into the present disclosure.

First Hit☐

L15: Entry 5 of 15

File: PGPB

Oct 9, 2003

DOCUMENT-IDENTIFIER: US 20030192066 A1
TITLE: Minimal adenoviral vector

Detail Description Paragraph:

[0317] 12. Chuah, M. K. L., T. Vandendriessche, and R. A. Mogan. 1995. Development and analysis of retroviral vectors expressing human factor VII as a potential gene therapy for hemophilia A. Human Gene Ther. 6: 1363-1377.

First Hit

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Print

L15: Entry 7 of 15

File: PGPB

Apr 17, 2003

DOCUMENT-IDENTIFIER: US 20030073652 A1

TITLE: Ex-vivo and in vivo factor XII gene therapy for hemophilia A and B

Summary of Invention Paragraph:

[0002] The invention relates to the use of recombinant Factor XII and truncated or mutated forms thereof, in gene therapy for conversion of inactive Factor VII to its active form in the treatment of Hemophilia A and B.

Detail Description Paragraph:

[0030] The adenoviral system with either full length Factor VII, or Factor VII from which the B-domain has been deleted, has been studied intensively. Expression levels using recombinant adenoviral vectors have been optimized in hepatocytes (Andrews et al, 1999), and studied when transfected into factor VII-deficient mice (Connelly et al, 1996; Connelly et al, 1998; Connelly et al, 1999). A minimal adenoviral vector, devoid of all viral genes, has been developed which theoretically avoids the intrinsic toxicity of the adenovirus (Balague et al, 2000). Such "mini-adenoviral" vectors have also been tested with Factor VIII in mice and dogs (Zhang et al, 1999). Ex-vivo gene therapy of primary fibroblasts with adenovirus mediated Factor VII has also been reported. The recombinant gene was placed into the virus in the test tube, and the gene-virus combination transfected into the cell. The cells were then implanted into the spleen of the recipient animal (Zatloukal et al, 1994). Adenovirus-mediated transfer of Factor IX has been associated with dose-limiting toxicity in monkeys (Lozier et al, 1999).

(FILE 'HOME' ENTERED AT 19:51:36 ON 01 MAR 2004)

FILE 'MEDLINE, CANCERLIT, BIOTECHDS, BIOSIS, EMBASE, CAPLUS' ENTERED AT
19:51:52 ON 01 MAR 2004

L1	1898 S FACTOR AND (BLOOD COAGULATION OR HEMOPHILI?) AND GENE THERAPY
L2	3410755 S REVIEW
L3	168 S L2 AND L1
L4	130 DUP REM L3 (38 DUPLICATES REMOVED)
L5	416539 S ADENOVIR? OR RETROVIR?
L6	42 S L5 AND L4

L6 ANSWER 39 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:741527 CAPLUS
DN 131:346059
TI Adeno-associated virus-mediated gene transfer of **factor IX** for
treatment of **hemophilia B** by **gene therapy**
AU Herzog, Roland W.; High, Katherine A.
CS Dep. Pediatrics Pathology, Medical Center, Univ. Pennsylvania,
Philadelphia, PA, USA
SO Thrombosis and Haemostasis (1999), 82(2), 540-546
CODEN: THHADQ; ISSN: 0340-6245
PB F. K. Schattauer Verlagsgesellschaft mbH
DT Journal; General Review
LA English
AB A **review** with 48 refs. is given on adeno-associated virus
(AAV)-mediated gene transfer of **factor IX** for treatment of
hemophilia B. **Gene therapy** strategies for
hemophilia B resulted in expression of **factor IX** in mice
and scale-up attempts to the canine and dog model were made. Long-term
expression of **factor IX** was achieved in dogs, the development of
inhibitory antibody was observed in some cases. The potential of the AAV
vectors to integrate into chromosomal DNA and the risk of germ-line
transmission is mentioned.

L6 ANSWER 38 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
AN 1999:741530 CAPLUS
DN 131:346061
TI Animal testing of **retroviral**-mediated **gene**
therapy for **factor** VIII deficiency
AU Greengard, Judith S.; Jolly, Douglas J.
CS Dep. Vaccines Gene Therapy, Chiron Technologies, Emeryville, CA, 94608,
USA
SO Thrombosis and Haemostasis (1999), 82(2), 555-561
CODEN: THHADQ; ISSN: 0340-6245
PB F. K. Schattauer Verlagsgesellschaft mbH
DT Journal; General Review
LA English
AB A **review** with 62 refs. is given on animal testing of
retroviral-mediated **gene therapy** for
factor VIII deficiency . Advantages and potential disadvantages
of **retroviral** vectors, and the status of **gene**
therapy for **hemophilia** in animal models is summarized.
Own unpublished results are also presented, describing the i.v. injection
of nonmurine packaging cell lines with high titers of **factor**
VIII vectors in dogs and rabbits, leading to **factor** VIII
expression in these animals.

L6 ANSWER 35 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN
 AN 2001:658526 CAPLUS
 DN 136:20
 TI Viral vector-mediated **gene therapy** for
hemophilia
 AU VandenDriessche, Thierry; Collen, Desire; Chuah, Marinee K. L.
 CS Center for Transgene Technology and Gene Therapy, Flanders Interuniversity
 Institute for Biotechnology-University of Leuven, Louvain, B-3000, Belg.
 SO Current Gene Therapy (2001), 1(3), 301-315
 CODEN: CGTUAH; ISSN: 1566-5232
 PB Bentham Science Publishers Ltd.
 DT Journal; General Review
 LA English
 AB A **review** with refs. is given. **Hemophilia** A and B are
 hereditary coagulation disorders that result from functional deficiencies
 of **factor VIII** (FVIII) or **factor IX** (FIX), resp.
 Current treatment consists of injections with blood plasma-derived or
 recombinant clotting factors. Despite the significant clin. benefits of
 protein replacement therapies, these do not constitute a cure and patients
 are still at risk of bleeding. Significant progress was made recently in
 the development of **gene therapy** for **hemophilia**
 . This was primarily due to the tech. improvements of existing vector
 systems and the development of new gene delivery methods. Therapeutic and
 sometimes physiol. levels of FVIII and FIX could be achieved in FVIII- and
 FIX-deficient mice and **hemophilic** dogs using different types of
 viral vectors. In these preclin. studies, long-term correction of the
 bleeding disorders and in some cases a permanent cure was realized.
 However, complications related to the induction of neutralizing antibodies
 or viral promoter inactivation often precludes stable phenotypic
 correction. Several **gene therapy** phase I clin. trials
 were initiated in patients suffering from severe **hemophilia** A or
 B. The results from the extensive pre-clin. studies and the preliminary
 clin. data are encouraging. It is likely that successful **gene**
therapy for **hemophilia** will become a reality at the
 beginning of this new millennium, serving as the trailblazer for
gene therapy of other diseases

L6 ANSWER 32 OF 42 CAPLUS COPYRIGHT 2004 ACS on STN

AN 2002:949415 CAPLUS

DN 139:94509

TI Adeno-associated virus-mediated gene transfer for **hemophilia B**

AU High, Katherine A.

CS Division of Hematology, The Children's Hospital of Philadelphia,
Philadelphia, PA, USA

SO International Journal of Hematology (2002), 76(4), 310-318

CODEN: IJHEEY; ISSN: 0925-5710

PB Carden Jennings Publishing

DT Journal; General Review

LA English

AB A **review**. **Hemophilia** is the bleeding diathesis caused

by mutations in the gene encoding **factor VIII** (

hemophilia A) or **factor IX** (**hemophilia B**).

Currently, the disease is treated by i.v. infusion of the missing purified clotting **factor**. The goal of gene transfer for treating

hemophilia is to achieve sustained expression of **factor**

VIII or **factor IX** at levels high enough to improve the symptoms

of the disease. **Hemophilia** has proven to be an attractive model

for those interested in gene transfer, and multiple gene-transfer

strategies are currently being investigated for the **hemophilias**.

The most promising preclin. studies have been with adeno-associated viral

vectors (AAV); introduction of AAV vectors expressing **factor IX**

into skeletal muscle or liver in **hemophilic** dogs has resulted in

the long-term expression of **factor IX** at levels that are

adequate to improve disease symptoms. Efforts to translate these findings

into the clin. arena have proceeded slowly because of the lack of prior

clin. experience with parenteral administration of AAV. In a staged

approach, AAV-**factor IX** (AAV-F.IX) was first administered at

doses of up to 1.8×10^{12} vector genomes/kg (vg/kg) into the

skeletal muscles of men with **hemophilia B**. This trial

established the safety of parenteral administration and also showed that

general characteristics of AAV transduction were similar in mice, dogs,

and humans. In an ongoing trial, AAV-F.IX is being administered into the

hepatic circulation of men with severe **hemophilia B**. The goal

of these studies is to identify a safe dose that reliably yields

circulating levels of **factor IX** >2% of normal levels in all

subjects. This goal has already been achieved in the **hemophilia**

B dog model; the ongoing study will determine whether a similar result can be

achieved in humans with **hemophilia B**.

L6 ANSWER 27 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN 97351864 EMBASE
DN 1997351864
TI **Gene therapy** for haemophilia.
AU Smith T.A.G.
CS T.A.G. Smith, Genetic Therapy Inc., 19 Firstfield Road, Gaithersburg, MD
20878, United States
SO Expert Opinion on Investigational Drugs, (1997) 6/11 (1685-1690).
Refs: 43
ISSN: 1354-3784 CODEN: EOIDER
CY United Kingdom
DT Journal; General Review
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
022 Human Genetics
025 Hematology
LA English
SL English
AB Progress rewards the development of a **gene therapy** protocol for the treatment of haemophilia has been substantial. Recent achievements include high level clotting **factor** expression in mice, dogs, and monkeys as well as phenotypic correction in both mouse and canine models of haemophilia. Studies using **adenoviral** (Ad) vectors have contributed to much of the recent success. However, the repertoire of gene transfer vehicles being applied to the development of **gene therapy** strategies for haemophilia has expanded. In particular, encouraging data have been generated from studies using recombinant adeno-associated virus (AAV) vectors. Progress toward human clinical trials has been inhibited by host immune responses which can limit the duration of therapy and prevent re-administration. Several strategies have demonstrated the feasibility of circumventing host immune responses, but more effective, clinically applicable procedures remain to be developed. While direct in vivo **gene therapy** strategies have generated significant progress, the results from ex vivo strategies have not been as encouraging.

L6 ANSWER 18 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN
 AN 2001308599 EMBASE
 TI **Gene therapy of hemophilia.**
 AU Schwaab R.; Oldenburg J.
 CS Dr. R. Schwaab, Inst. Exp. Haematol./Transfus. Med., Sigmund-Freud-Str.
 25, 53105 Bonn, Germany. rainerschwaab@ukb.uni-bonn.de
 SO Seminars in Thrombosis and Hemostasis, (2001) 27/4 (417-424).
 Refs: 50
 ISSN: 0094-6176 CODEN: STHMBV
 CY United States
 DT Journal; General Review
 FS 022 Human Genetics
 025 Hematology
 036 Health Policy, Economics and Management
 037 Drug Literature Index
 LA English
 SL English
 AB **Hemophilia** A and B are X-linked bleeding disorders caused by mutations within the **factor** VIII and **factor** IX genes, respectively. Although both disorders can be easily treated by substitution with concentrates of functional **factor** VIII and **factor** IX, considerable effort has been undertaken to develop a **gene therapy** for **hemophilia** in order to improve patients' life quality and reduce high costs of therapy. The principle of **gene therapy** is the introduction of an intact copy of the **factor** VIII/**factor** IX gene in somatic cells, compensating for the defective gene. To do this, **retroviral**, **adenoviral**, and adeno-associated virus (AAV) vector systems, among others, were used. Encouraged by the results of preliminary experiments using preponderant mouse and canine models, three clinical phase I studies on **hemophilia** A and B patients have been initiated, one of which has been preliminarily reported successful.

L6 ANSWER 6 OF 42 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
 on STN
 AN 2003390008 EMBASE
 TI The promise of third-generation recombinant therapy and **gene therapy**.
 AU Manno C.S.
 CS Dr. C.S. Manno, Division of Hematology, Children's Hospital of Philadelphia, 34th St and Civic Center Blvd, Philadelphia, PA 19104, United States
 SO Seminars in Hematology, (2003) 40/3 SUPPL. 3 (23-28).
 Refs: 12
 ISSN: 0037-1963 CODEN: SEHEA3
 CY United States
 DT Journal; General Review
 FS 025 Hematology
 037 Drug Literature Index
 038 Adverse Reactions Titles
 039 Pharmacy
 LA English
 SL English
 AB Recombinant **factor** VIII and IX products have well-established efficacy and safety records. However, concerns about the possibility of viral transmission have prompted efforts to develop recombinant products that are free of added human and animal proteins. The currently licensed second-generation recombinant **factor** VIII concentrates were introduced in 2000. Two new third-generation products, manufactured without any human- or animal-derived materials, are currently in development and clinical testing. As an alternative to exogenous **factor** replacement, **gene therapy** is under investigation for use in the treatment of **hemophilia**. **Gene therapy** involves the stable insertion of a functional gene for long-term expression and secretion of endogenous **factor** VIII or IX protein. Methods used to date have been based on **retroviral**, **adenoviral**, and adeno-associated viral vectors, as well as nonviral electroporation. Three phase I trials using these approaches have been completed as of 2002, and one more is ongoing. This article reviews the results of recent clinical studies investigating third-generation recombinant products and gene-based approaches to **hemophilia** treatment. .COPYRGT. 2003 Elsevier Inc. All rights reserved.

L6 ANSWER 1 OF 42 MEDLINE on STN
 AN 1998039375 MEDLINE
 DN PubMed ID: 9372106
 TI **Gene therapy** for the **hemophilias**.
 AU Fallaux F J; Hoeben R C
 CS Department of Internal Medicine, University Hospital Utrecht, The Netherlands.
 SO Current opinion in hematology, (1996 Sep) 3 (5) 385-9. Ref: 37
 Journal code: 9430802. ISSN: 1065-6251.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 (REVIEW, TUTORIAL)
 LA English
 FS Priority Journals
 EM 199712
 ED Entered STN: 19980109
 Last Updated on STN: 19990129
 Entered Medline: 19971223
 AB This **review** discusses the progress of **gene therapy** for the **hemophilias**. The development of **gene therapy** for **hemophilia A** has been more problematic than that for **hemophilia B**. It is now well established that reduced expression of the human clotting **factor VIII** cDNA is caused by transcriptional repression. Multiple sequences within the **factor VIII** cDNA are involved. So far, attempts to improve the **factor VIII** cDNA expression have been unsuccessful. However, improved **retroviral** vectors and **adenovirus**-based vectors have been constructed that increase **factor VIII** expression. The use of these vectors has resulted in clinically relevant levels of human **factor VIII** in mice and **hemophilic** dogs. Thus, **gene therapy** for **hemophilia A** has reached the same developmental stage as that for **hemophilia B**. If further improvements can increase the persistence of expression and decrease the immunologic responses, phase I clinical trials in human individuals can be considered.